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(54) Title: PROCESS FOR THE PREPARING OF HARDCAPSULE FORMULATION CONTAINING LANSOPRAZOLE

(57) Abstract: The present invention relates to a method for producing a new hard capsule preparation containing lansoprazole, which has excellent stability and is administered in an easy and simple manner. The method comprises the steps of: dissolving or dispersing lansoprazole in oil or fatty acid; adding the lansoprazole solution to a swollen polymer solution containing an emulsifying agent and an alkalifying agent; stirring the resulting mixture; adding additives to the stirred material to produce an emulsion; injecting the emulsion into an aqueous calcium chloride solution to form a film on a granule of the emulsion; filtering and washing the granule to remove calcium ions; freeze-drying the washed granule to produce a pellet; forming a film and an enteric coating layer on the pellet; forming a film and an enteric coating layer on the pellet; and filling the resulting pellet in a hard gelatin capsule.

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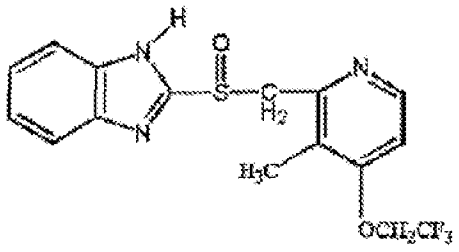
PROCESS FOR THE PREPARING OF HARDCAPSULE FORMULATION CONTAINING LANSOPRAZOLE

Technical Field

The present invention relates to an acid unstable lansoprazole-containing hard capsule preparation with improved stability and maximized therapeutic effects, and also a method for preparing the same. An object of the present invention is to provide a new preparation, which allows complete prevention of the reduction of drug activity caused by gastric acid upon its oral administration, and easy absorption of a drug in the small intestine.

Lansoprazole, which is a proton pump inhibitor (gastric secretion inhibitor), was approved for putting on the market by the US Food and Drug Administration (FDA) in May 1995, and has been sold under the trademark of Lanston from December 1995 in Korea. Lansoprazole is one of benzimidazole derivatives such as omeprazole, and has the chemical name of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole. Lansoprazole is represented by the following formula:



Background Art

Lansoprazole is administered in the form of a capsule formulated as an enteric-coated granule, since it is unstable in acid and thus decomposed by gastric acid before absorption. Lansoprazole is a prodrug that exhibits pharmacological action by metabolism into AG-1812 and AG-2000 as metabolites of an active sulfenamide form under an acidic atmosphere of gastric parietal cell canaliculi. These metabolites inactivate a proton pump by binding with a sulfhydryl group of H^+/K^+-exchanging ATPase, thereby preventing intracellular potassium-hydrogen exchange. At this time, the sulfenamide metabolites irreversibly form a covalent bond with the H^+/K^+-exchanging ATPase, so that gastric acid secretion is inhibited until an enzyme is synthesized again, and thus, they show a long duration of action of more than 24 hours. The reduction of gastric acid secretion by lansoprazole acts as negative-feedback mechanisms, which results in an increase in serum gastrin level. Furthermore, lansoprazole increases stomach PH to reduce pepsin secretion and activity, and also increases serum pepsinogen level.

Meanwhile, lansoprazole has an inhibitory effect against *Helicobacter pylori* present in patients with stomach and duodenal ulcer. This effect attributes to an increase in concentration and effects of antibiotics used in combination with lansoprazole, such as amoxicillin, clarithromycin and the like, by the inhibition of gastric acid secretion and thus the reduction of intragastric acidity, or to a direct antibiotic effect of lansoprazole, but its clear mechanism was not yet established.

Upon oral administration, lansoprazole formulated as a

capsule containing enteric-coated granules is absorbed within 30 minutes and reaches the peak plasma level after about 1.5-3 hours. Its bioavailability is 80-85%. Upon administration of lansoprazole with food, Delhotal-Landes, et al. reported that its absorption was delayed and its peak blood concentration and bioavailability were reduced, but other studies reported that its bioavailability was not influenced. When used in combination with an antacid, the bioavailability of lansoprazole is not influenced. The serum protein-binding rate of lansoprazole is 97-99% and the volume of distribution is 0.45 l/kg. Absorbed lansoprazole in blood passes through a parietal cell's basal membrane and converted into AG-1812 and AG-2000 as metabolites of an active form under an acidic condition of the secretory canaliculus. Moreover, in the liver, lansoprazole is metabolized into lansoprazole sulfone, hydroxy lansoprazole, lansoprazole sulfide, and lansoprazole hydroxysulfone. The metabolites metabolized in the liver are mostly excreted in bile and only 14-25% of them are excreted in urine. Non-metabolized lansoprazole is detected in urine and feces at a small amount. The elimination half-life is 1.3-1.7 hours, and in the case of liver cirrhosis or hepatitis patients, it is extended to 6.1-7.2 hours. Renal insufficiency has little or no effect on pharmacokinetics of this drug.

In spite of its excellent therapeutic effect, since lansoprazole having such properties is highly sensitive to an acid, there are many difficulties in formulating lansoprazole. PCT patent publication WO 2001/28559 discloses a method of formulating lansoprazole using crospovidone, sodium hydroxide and potassium hydroxide. Korean patent laid-open Publication No. 2001-114225

discloses a method of formulating lansoprazole using a basic amino acid as an additive. However, in such methods, the dissolution of an enteric coating layer caused by an alkalifying agent can be rather induced due to high wettability, and also the instability caused by gastric juice can be increased. Korean patent laid-open publication No. 2002-20974 discloses a method of stabilizing a drug using ethylcellulose. However, this method cannot be regarded as a preferred method since polymer swelling caused by gastric juice can occur so that drug stability can be influenced. Furthermore, this method is disadvantageous in that drug release can be delayed since ethylcellulose is insoluble in water. Korean patent laid-open publication No. 2000-76232 discloses a method of stabilizing a drug by encapsulating the drug with beta-cyclodextrin using an amino acid as an alkalifying agent. However, this method cannot be regarded as a recommendable method since the stability of the drug can vary depending on an encapsulated state.

Disclosure of Invention

Accordingly, the present inventors have conducted studies in attempts to stabilize lansoprazole unstable in an acid by means of an alkalifying agent and to make a preparation process simple so as to increase productivity.

The present invention provides a method for preparing a lansoprazole-containing hard capsule preparation, which comprises the steps of: dissolving or dispersing lansoprazole in oil or fatty acid; adding the lansoprazole solution to a swollen polymer solution containing an

emulsifying agent and an alkalifying agent; stirring the resulting mixture; adding additives to the stirred material to produce an emulsion; injecting the emulsion into an aqueous calcium chloride solution to form a film on a granule of the emulsion; filtering and washing the granule to remove calcium ions; freeze-drying the washed particle to produce a pellet of a 100-1500 μm size; forming a film and an enteric coating layer on the pellet; and filling the resulting pellet in a hard gelatin capsule.

In brief, the present invention provides a pellet preparation, and a method of preparing the same, which comprises the steps of: dissolving or dispersing lasoprazole in oil or fatty acid; adding an emulsifying agent to the lasoprazole solution to produce a milky emulsion; adding pharmaceutically acceptable additives to the emulsion; stirring the resulting emulsion at high speed to produce a uniform solution; and injecting the uniform solution into a reaction solution through an injector.

Examples of oil suitable for use in the preparation of the pellet according to the present invention include esters, such as stearyl glycyrrhetinate, tocopheryl acetate, panthenol, phosphatidylcholine, glyceryl stearate, captylic/capric triglyceride, cetyl octanolate, isopropyl myristate, ceteatyl octanoate, butylene glycol dicaptylate/dicaprate, hydrogenated castor oil, monoglycerides, diglycerides, triglycerides, and the like; and vegetable materials, such as beeswax, carnauba wax, olive oil, jojoba oil, hybrid sunflower (Helian thus annuus) oil and the like. Preferred examples of oils which can be used in the present invention include mineral oil, squalene, squalane, monoglycerides, diglycerides,

triglycerides, middle chain glycerides, myglyol, cremophor, hydrogenated castor oil, corn oil, soybean oil, sesame oil, cottonseed oil and fat-soluble Vitamin. The weight ratio between the oil or fatty acid and lansoprazole is 0.5-5:1, and preferably 0.5-2:1 in view of dissolution or dispersion.

Examples of the fatty acid that can be used in the present invention include linoleic acid, stearic acid, oleic acid, cetyl alcohol, stearyl alcohol, myristic acid, lauric acid and the like.

Examples of the emulsifying agent, which can be added to the mixture of lansoprazole and oil to produce the uniform emulsion, include sodium lauryl sulfate, hydroxypropylmethylcellulose (HPMC), hydroxypropylcelulose (HPC), carboxymethylcellulose and sodium or calcium salts thereof, carrageenan, alginic acid and magnesium, sodium or calcium salt thereof, povidone, polyvinyl alcohol, tragacanth gum, chitosan, chitin, Tween, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, oleyl alcohol, lecithin, diethanolamine, cholesterol, poloxamer, trolamine, wax and the like.

The additives that can be used to maintain a shape of the pellet include starch, pregelatinized starch, lactose, mannitol, sorbitol, sucrose, dextrin, carbomer 910, 934, 934P, 940, 941 or 1342, calcium carbonate, calcium phosphate dibasic or tribasic, calcium sulfate, talc and the like.

The reaction solution that is used to form the pellet in the present invention is an aqueous calcium solution, which reacts with a material capable of forming a film to solidify the film material present in a liquid state, thereby maintaining the film material at a certain shape.

Sodium alginate serving as an emulsifying agent and also a film-forming material in the present invention has a property in that it is solidified upon contact with calcium ions. When sodium alginate is in contact with divalent metal ions, such as calcium ions, ion exchange instantaneously occurs so that two molecules of sodium and one molecule of a calcium ion are substituted with each other. As a result, sodium alginate that is soluble in water is substituted with a calcium ion so that it is converted into calcium alginate while being solidified in an aqueous solution. Time taken for this reaction is known to be about 7 minutes, and the adjustment of reaction time and calcium ion concentration allows preparation of pellets having various shapes and release patterns.

In preparing the pellet according to the present invention, an injection nozzle can be used to produce a bead of a desired size. In this case, a lansoprazole-containing pellet preparation with a diameter of 0.3-2.5 mm can be produced.

As a matrix base forming the pellet, there is preferably used one or more selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), carboxymethylcellulose, and sodium or calcium salt thereof, carraginan, anginic acid, and magnesium, sodium and calcium salt thereof, povidone, polyvinylalcohol, tragacanth gum, chitosan, and chitin.

As an additive for maintaining the pellet shape, there is preferably used one or more selected from the group consisting of starch, pregelatinized starch, lactose, mannitol, sorbitol, sucrose, dextrin, Carbomer 910, 934, 934P, 940, 941 or 1342, calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium

sulfate and talc.

Furthermore, the present invention relates to a method of producing a lansoprazole-containing hard capsule preparation, which comprises the steps of: producing an inactive fine granule with a particle size of 0.2-0.7 mm which contains starch and sucrose, or only sucrose; dissolving or dispersing a pharmacologically active substance selected from the group consisting of omeprazole, lansoprazole, pantoprazole and rabeprazole, hydroxypropylmethylcellulose (HPMC) as a binder, methyl glucamine as an alkalifying agent, and talc, in water and alcohol, or in only water, thereby producing a solution; coating the inactive fine granule with the solution, thereby producing a spherical pellet having a diameter of 0.3-2.0 mm; forming a protective coating layer and an enteric coating layer on the pellet, thereby producing an enteric soluble pellet having a particle size of 0.5-2.5 mm; and filling the enteric soluble pellet in a hard capsule.

The present invention, which realizes the granulation and sphericalization of lansoprazole using various seeds after dissolving or dispersing lansoprazole in a suitable solvent, can overcome the problem of low yield caused in the production of similar preparations according to the prior art, thereby minimizing the loss of raw materials. Furthermore, in the present invention, the dissolution of lansoprozole is easily conducted by addition of a suitable excipient and solvent. And in the present invention, the protective coating layer and the enteric coating layer are formed on the granulated and sphericalized drug by means of a suitable base so that the present invention is advantageous in that a process can become very simple.

In the present invention, lansoprazole is used after dissolution or dispersion in water and alcohol or only water, and the solubility of lansoprazole can be adjusted according to a change in its mixing ratio. In the present invention, the mixing ratio between water and alcohol is 1:1, 0.8:1, 0.6:1, 0.5:1, 0.4:1, 0.2:1, 0:1 or the like. The more the amount of alcohol, the solubility of lansoprazole is slightly increased but its stability is insufficient.

In the present invention, in order to maximize the stability of lansoprazole, there is used a method wherein the alkalifying agent is added to a core containing the drug, and the protective coating layer serving to prevent the drug from being contacted with the enteric coating layer is formed. Moreover, it was found that talc allowing effective prevention of the adhesion phenomenon between particles in coating forms an alkaline atmosphere upon mixing with lansoprozole. In other words, when talc is added, it maximizes the stability of lansoprazole in cooperation with the alkalifying agent.

Meanwhile, talc that is the hydrated magnesium silicate is a white-light gray colored, fine, crystalline powder, and substantially insoluble in water, ethanol or ether. For this reason, it is a highly stable, neutral, lubricative excipient, which does not influence the titer of an active substance.

Concretely, in the preparing method according to the present invention, an inactive fine granule is prepared from starch and sucrose. Meanwhile, lansoprazole, methyl glucamine (meglumine) as an alkalifying agent, hydroxypropylmethylcellulose or derivatives thereof are completely dissolved or dispersed in a suitable solvent,

after which the resulting solution is combined with the inactive fine granule. At this time, talc as an excipient for additional stabilization may be added to the solution at a suitable amount. A protective coating layer is formed on the granule combined with lansoprazole using a film coating base. Then, an enteric coating layer is formed so as to produce a preparation having a particle size of 0.5-2.5 mm. This preparation can be made to have the titer of 80-100 mg per gram.

Best Mode for Carrying Out the Invention

The present invention is an enteric-coated fine granule containing lansoprazole and the like, which is filled in a hard gelatin capsule at a desired amount for its convenient administration. The hard capsule preparation according to the present invention is orally administered at a dosage of 30 mg once daily. The present invention will hereinafter be described in further detail by examples. It should however be borne in mind that the present invention is not limited to or by the examples.

Example 1

Lansoprazole as a drug is mixed with oil, and introduced in a swollen polymer solution in which sodium alginate, HPMC, and methyl glucamine (meglumine) are dissolved. After being stirred with a homogenizer for 10 minutes, the resulting mixture is added with starch and lactose, followed by being stirred for 10 minutes, thereby producing a milky emulsion. The emulsion is supplied at a constant rate using a peristaltic pump while it is injected

into an aqueous solution of 2-4% calcium chloride ($CaCl_2$) by means of a designed nozzle. After injection, the resulting material is left to stand for about 15 minutes, and filtered through a 100-mesh sieve, and then washed with pure water to remove calcium ions remaining in a pellet. After removing moisture, the resulting material is freeze-dried to give a pellet having a size of about 100-1500 μm. Next, a film is coated on the pellet using hydroxypropylmethylcellulose as a base by means of a fluidized bed coater. Following this, an enteric coating layer is formed on the surface of the resulting pellet using a solution in which hydroxypropylmethylcellulose phthalate or Eudragit L-100 or L100-55 is dissolved in a suitable solvent. This gives a lansoprazole-containing pellet with maximized stability. The pellet obtained as described above is filled in a hard gelatin capsule.

Table 1: Composition of lansoprazole-containing pellet prepared from alginate bead according to Example 1 (unit: gram)

Component	Core	Protective coating	Enteric coating
Lansoprazole	30.0	-	-
Methyl glucamine(Meglumine)	7.0	-	-
Sodium alginate	1.5	-	-
Hydroxypropylmethylcellulose	1.5	16.5	-
Soybean oil	40.0	-	-
Lactose	51.0	-	-
Corn starch	51.0	-	-

Hydroxypropylmethylcellulose phthalate	-	-	17.3
Triacetin	-	-	2.7
Total	182.0	200.0	230.0

Examples 2-7

Examples 2-7 are compositions of a lansoprazole-containing core prepared using an alginate bead, and the preparation, protective coating and enteric coating of the core are carried out in the same manner as in Example 1.

Table 2: Compositions of lansoprazole-containing pellet prepared from alginate bead according to Examples 2-7

(unit: % by weight)

Component	Exam.2	Exam.3	Exam.4	Exam.5	Exam.6	Exam.7
Lansoprazole	30.0	30.0	30.0	30.0	30.0	30.0
Methyl glucamine	3.0	4.0	5.0	10.0	12.0	15.0
Sodium alginate	0.5	1.5	1.5	1.5	1.5	1.5
Hydroxypropylmethyl cellulose	0.5	1.5	1.5	1.5	1.5	1.5
Soybean oil	40.0	40.0	40.0	40.0	40.0	40.0
Lactose	53.0	52.5	52.0	49.5	48.5	47.0
Corn starch	53.0	52.5	52.0	49.5	48.5	47.0
Total	182.0	182.0	182.0	182.0	182.0	182.0

Comparative Example 1

This example is carried out in the same manner in

Example 1 except that meglumine is not used.

Table 3: Composition of lansoprazole-containing pellet prepared from alginate bead according to Comparative Example 1 (unit: gram)

Component	Core	Protective coating	Enteric coating
Lansoprazole	30.0	-	-
Sodium alginate	1.5	-	-
Hydroxypropylmethylcellulose	1.5	16.5	-
Soybean oil	47.0	-	-
Lactose	51.0	-	-
Corn starch	51.0	-	-
Hydroxypropylmethylcellulose phthalate	-	-	17.3
Triacetin	-		2.7
PEG6000	-	1.7	-
Total	182.0	200.0	230.0

Test Example 1: Test of stability of preparations

The stability test results on the respective lansoprazole-containing enteric soluble pellets prepared in Examples 1-7 and Comparative Example 1 are as follows.

The stability test was carried out according to a test method described in Korea Pharmacopeia. In the case of Comparative Example 1, there was observed a phenomenon in which the modification of the drug occurs during preparation. Also, during coating and stability test, activity of the drug was reduced by about 30%. As a result, it can be found that, when a drug that is unstable in acids is formulated as in the present invention, there is necessary an alkalifying agent allowing stabilization of

the drug. Furthermore, the selection of the solvent used in the production of a preparation is very important.

Table 4: Stability test results on lansoprazole-containing pellets produced in Examples 1-7 (unit: %)

Test items	Storage condition	Exam.1	Exam.2	Exam.3	Exam.4	Exam.5	Exam.6	Exam.7
Configuration	Room temp.	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)
	40℃,75%R.H. (30days, 60days)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)
Content	Room temp.(30days)	100	99	100	100	100	100	100
	Room temp.(60days)	99	96	98	98	99	99	99
	40℃,75%R.H.(30days)	99	91	94	97	99	98	99
	40℃,75%R.H.(60days)	99	89	92	97	95	97	98
Acid-Resistance	Room temp.(30days)	99	97	98	98	99	98	98
	Room temp.(60days)	99	93	97	98	95	97	99
	40℃,75%R.H.(30days)	98	88	94	98	95	94	96
	40℃,75%R.H.(60days)	97	86	91	96	95	94	96
Dissolution rate	Room temp.(30days)	98	96	99	99	99	99	99
	Room temp.(60days)	97	95	95	95	97	95	95
	40℃,75%R.H.(30days)	98	92	90	96	97	94	94

(-): No change

Example 8

200 g of sucrose sieved to have a desired size is used as an inactive granule by itself, and generally, a particle size of sucrose, which is most suitable for use in this Example, is about 0.2-0.7 mm.

Table 5: Composition of lansoprazole-containing enteric granule (unit: gram)

Component	Core	Protective coating	Enteric coating
Inactive fine granule	125.1		
Lansoprazole	30.0	-	-
Methyl glucamine(Meglumine)	7.5	-	-
Hydroxypropylmethylcellulose	3.8	16.5	-
PEG6000	0.4	1.7	-
Corn starch	5.0	-	27.3
Hydroxypropylmethylcellulose phthalate	-	-	2.7
Triacetin	-	-	-
Talc	5.0	-	-
Titan dioxide	5.0	-	-
Total(weit, g)	181.8	200.0	230.0

Lansoprazole, methyl glucamine, and hydroxypropylmethylcellulose or derivatives thereof are completely dissolved or dispersed in a mixture of purified water, acetone and ethanol. Then, with fluidization of the inactive fine sucrose granule, the resulting solution is

coated on the inactive fine sucrose granule together with talc by means of a fluidized bed coater, thereby producing a lansoprazole-containing pellet having a particle size of about 0.5-2.5 mm. Then, in order to prevent the pellet from being contacted with an enteric coating base, a protective coating layer is formed on the pellet using hydroxypropylmethylcellulose, and in order to render the pellet more stable under an acidic condition such as gastric juice, an enteric coating layer serving to completely isolate the pellet from gastric juice is formed on the pellet. The enteric coating layer is most preferably formed on the surface of the pellet to have a thickness of at least 0.01-0.05 mm. Examples of a coating base that can be used in forming the enteric coating layer include hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, and derivatives thereof. Also, a methacrylic acid copolymer that is commercially available under the trademark of Eudragit L or S may be used to form the enteric coating layer. Preferably, Eudragit L100-55 or hydroxypropylmethylcellulose phthalate (HP55) is used in the present invention.

Examples 9-14

Examples 9-14 are compositions of a core containing lansoprazole, and the preparation, protective coating and entric coating of the core are carried out in the same manner as in Example 8.

Table 6: Compositions of lansoprazole-containing pellets prepared according to Examples 9-14 (unit: gram)

Component	Exam.9	Exam.10	Exam.11	Exam.12	Exam.13	Exam.14
Inactive fine granule	129.8	128.8	127.8	122.8	120.8	117.8
Lansoprazole	30.0	30.0	30.0	30.0	30.0	30.0
Methyl glucamine	3.0	4.0	5.0	10.0	12.0	15.0
Hydroxypropylmethylcellulose	3.8	3.8	3.8	3.8	3.8	3.8
PEG6000	0.4	0.4	0.4	0.4	0.4	0.4
Corn starch	5.0	5.0	5.0	5.0	5.0	5.0
Talc	5.0	5.0	5.0	5.0	5.0	5.0
Titan dioxide	5.0	5.0	5.0	5.0	5.0	5.0
Total	182.0	182.0	182.0	182.0	182.0	182.0

Comparative Example 2

This example is carried out in the same manner as Example 8 except that meglumine is not used.

Table 7: Composition of lansoprazole-containing enteric soluble granule (unit: gram)

Component	Core	Protective coating	Enteric coating
Inactive fine granule	125.1		
Lansoprazole	30.0	-	-
Hydroxypropylmethylcellulose	3.8	16.5	-
PEG6000	0.4	1.7	-
Corn starch	5.0	-	27.3
Hydroxypropylmethylcellulose phthalate	-	-	2.7
Triacetin	-	-	-
Talc	5.0	-	-
Titan dioxide	5.0	-	-
Total(weit, g)	174.3	200.0	230.0

Test Example 2

The stability test results on the respective lansoprazole-containing enteric soluble pellets prepared in Examples 8-14 and Comparative Example 2 are as follows.

The stability test on the respective pellets was carried out according to a test method described in Korea Pharmacopeia. As can be seen in Table 8 below, it can be found that all Examples 8-14 are highly stable preparations. On the other hand, in the case of Comparative Example 2, there was observed a phenomenon in which the modification of the drug occurs during preparation. Also, during coating and stability test, activity of the drug was reduced by about 30%. As a result, it can be found that, when a drug that is unstable in acids is formulated as in the present invention, there is necessary an alkalifying agent allowing stabilization of the drug. Furthermore, the selection of the solvent used in the production of a preparation is very important.

Table 8: Stability test results on lansoprazole-containing pellets produced in Examples 8-14 (unit: %)

Test items	Storage condition	Exam. 8	Exam. 9	Exam. 10	Exam. 11	Exam. 12	Exam. 13	Exam. 14
Configura t-ion	Room temp. (30 days)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)
	40°C, 75%R.H. (60 days)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)	Sphere (-)
Content	Room temp. (30 days)	100	99	99	100	100	100	99
	Room temp. (60 days)	99	94	97	98	99	99	98

	40°C, 75%R.H. (30 days)	96	90	94	97	99	98	92
	40°C, 75%R.H. (60 days)	95	89	90	97	97	95	88
Acid resistance	Room temp. (30 days)	98	97	97	98	99	98	94
	Room temp. (60 days)	98	93	96	98	96	96	90
	40°C, 75%R.H. (30 days)	96	88	90	97	96	92	88
	40°C, 75%R.H. (60 days)	96	85	87	95	95	90	87
Dissolution rate	Room temp. (30 days)	99	99	99	99	99	99	99
	Room temp. (60 days)	99	98	95	95	98	95	95
	40°C, 75%R.H. (30 days)	98	92	90	94	96	93	94
	40°C, 75%R.H. (60 days)	97	86	88	95	95	92	93

Industrial Applicability

As described above, the present invention provides the lansoprazole-containing hard capsule preparation, which is stable and administered in an easy and simple manner. According to the present invention, this lansoprazole-containing hard capsule preparation can be produced by a method comprising the steps of: producing an emulsion containing lansoprazole, oil or fatty acid, an emulsifying agent, an alkalifying agent and other additives; injecting

the emulsion into an aqueous calcium chloride solution to form a film on a granule of the emulsion; freeze-drying the resulting granule to produce a pellet; and forming a protective coating layer and an enteric coating layer on the pellet.

What Is Claimed Is:

1. A method for preparing a lansoprazole-containing hard capsule preparation, which comprises the steps of:

dissolving or dispersing lansoprazole in oil or fatty acid;

adding the lansoprazole solution to a swollen polymer solution containing an emulsifying agent and an alkalifying agent;

stirring the resulting mixture;

adding additives to the stirred material to produce an emulsion;

injecting the emulsion into an aqueous calcium chloride solution to form a film on a granule of the emulsion;

filtering and washing the granule to remove calcium ions;

freeze-drying the washed granule to produce a pellet of a 100-1500 μm size;

forming a film and an enteric coating layer on the pellet; and

filling the resulting pellet in a hard gelatin capsule.

2. The method of Claim 1, wherein the alkalifying agent is methyl glucamine.

3. The method of Claim 1, wherein the mixing ratio between the lansoprazole and the oil or fatty acid is 0.5-5:1.

4. The method of Claim 1, wherein the oil is one or more selected from the group consisting of esters, including stearyl glycyrrhetinate, tocopheryl acetate, panthenol, phosphatidylcholine, glyceryl stearate, captylic/capric triglyceride, cetyl octanolate, isopropyl myristate, ceteatyl octanoate, butylene glycol dicaptylate/dicaprate, hydrogenated castor oil, monoglycerides, diglycerides, triglycerides, and the like; vegetable materials, including beeswax, carnauba wax, olive oil, jojoba oil, hybrid sunflower (Helian thus annuus) oil and the like; mineral oil, squalene, squalane, monoglycerides, diglycerides, triglycerides, middle chain glycerides, myglyol, cremophor, hydrogenated castor oil, corn oil, soybean oil, sesame oil, cottonseed oil and fat-soluble Vitamin.

5. The method of Claim 1, wherein the fatty acid is one or more selected from the group consisting of linoleic acid, stearic acid, oleic acid, cetyl alcohol, stearyl alcohol, myristic acid, isopropyl myristic acid, and lauric acid.

6. The method of Claim 1, wherein the pellet is made to have a diameter of 0.3-2.5 mm by means of an injection nozzle.

7. The method of Claim 1, wherein a hydrophilic polymer base of forming the pellet is one or more selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), carboxymethylcellulose, and sodium or calcium salt thereof, carraginan, anginic acid, and magnesium, sodium and calcium

salt thereof, povidone, polyvinyl alcohol, tragacanth gum, chitosan, and chitin.

8. The method of Claim 1, wherein the emulsifying agent serving to promote the dissolution is one or more selected from the group consisting of sodium lauryl sulfate, hydroxypropylmethylcellulose (HPMC), hydroxypropylcelulose (HPC), carboxymethylcellulose and sodium or calcium salts thereof, carrageenan, alginic acid and magnesium, sodium or calcium salt thereof, povidone, polyvinyl alcohol, tragacanth gum, chitosan, chitin, Tween, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, oleyl alcohol, lecithin, diethanolamine, cholesterol, poloxamer, trolamine, and wax.

9. The method of Claim 1, wherein the additives serving to maintain a shape of the pellet is one or more selected from the group consisting of starch, pregelatinized starch, lactose, mannitol, sorbitol, sucrose, dextrin, carbomer 910, 934, 934P, 940, 941 or 1342, calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium sulfate, and talc.

10. A method of producing a lansoprazole-containing hard capsule preparation, which comprises the steps of:

producing an inactive fine granule with a particle size of 0.2-0.7 mm which contains starch and sucrose, or only sucrose;

dissolving or dispersing a pharmacologically active substance selected from the group consisting of omeprazole, lansoprazole, pantoprazole and rabeprazole,

hydroxypropylmethylcellulose (HPMC) as a binder, methyl glucamine as an alkalifying agent, and talc, in water and alcohol, or in only water, thereby producing a solution;

coating the inactive fine granule with the solution, thereby producing a spherical pellet having a diameter of 0.3-2.0 mm;

forming a protective coating layer and an enteric coating layer on the pellet, thereby producing an enteric soluble pellet having a particle size of 0.5-2.5 mm; and

filling the intestine-soluble pellet in a hard capsule.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/00835

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBMED

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, E	KR 2003-0065825 (KOREA RESEARCH INST. CHEM. TECH.) 09 AUGUST 2003 see the whole document	1-10
A	US 2002-0137771 A1 (TAKEDA CHEM. IND. LTD.) 26 SEPTEMBER 2002 see the whole document	1-10
A	US 2001-0025107 A1 (TIMOTHY J. BARBERICH et al) 27 SEPTEMBER 2001 see the whole document	1-10
A	US 2002-0160046 A1 (JOSEPH R. ROBINSON et al) 31 OCTOBER 2002 see the whole document	1-10
A	KR 92-8161 (HANMI PHARM. CO. LTD.) 24 SEPTEMBER 1992 see the whole document	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 NOVEMBER 2003 (27.11.2003)	28 NOVEMBER 2003 (28.11.2003)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR03/00835

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